Short, Gram-Scale Syntheses of β- and γ-Lycorane Using Two Distinct Photochemical Approaches

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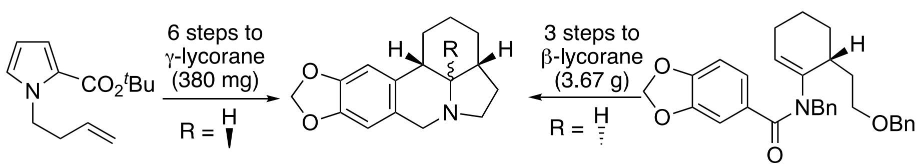
Supporting Information Placeholder



ABSTRACT: The synthesis of two diastereomeric members of the lycorane alkaloid family is reported. Although the routes are quite different in their approach, both involve the use of photochemistry as key steps, enabling the synthesis of gram quantities in the case of β-lycorane.

The *Amaryllidaceae* family of plants has a long history of yielding alkaloids with potential medicinal value.[1] These bulbous plants, including daffodils and snowdrops, have yielded over 300 different alkaloids including galanthamine **1**, crinine **2** and lycorine **3**. Galanthamine was approved by the FDA in 2001 for the treatment of Alzheimer's disease. Lycorine **3** and the more highly saturated lycoranes **4**–**6** have been shown to be inhibitors of cell growth and cell division and screened for antitumor activity in human cell lines[2] and as such a number of total synthesis have been investigated[3] (Figure 1).

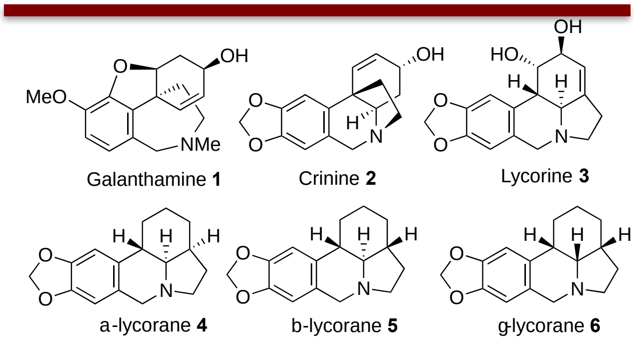
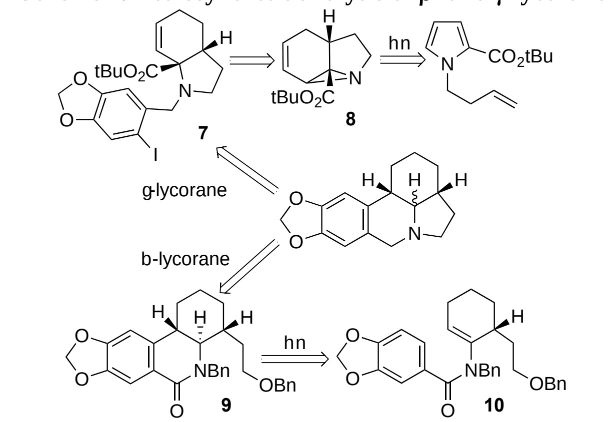


Figure 1. Selection of alkaloids from *Amaryllidaceae* family

As part of a program investigating the use of synthetic photochemistry as a tool for drug discovery, we became interested in developing efficient and scalable routes towards the lycorine alkaloids. Initially, we focussed on β- and γ-lycorane, which differ in the stereochemistry of the central hydrogen adjacent to the ring nitrogen. Although there have been a number of syntheses reported for the lycoranes we were keen to develop short and productive routes to these alkaloids, enabling their generation in gram quantities. In particular we were keen to demonstrate the power of organic photochemistry in the generation of this tetracyclic framework.

For γ-lycorane **6** we chose a route involving Heck cyclization of the iodide **7** as this would allow formation of the all *cis* stereochemistry after decarboxylation and iminium ion reduction (Scheme 1). The aryl iodide **7** should be readily available from the tricyclic aziridine **8**, which itself could be prepared by pyrrole photocycloaddition chemistry previously developed by us.[4]

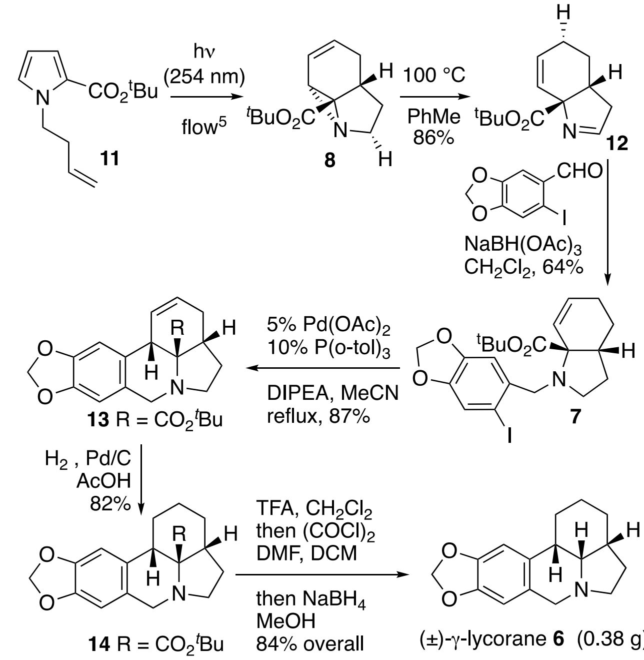
Scheme 1. Retrosynthetic analysis of β- and γ-lycorane



Short-wave (254 nm) irradiation of simple pyrrole **11** in an FEP flow reactor system gave access to the tricyclic aziridine **8** (Scheme 2). In batch this two-photon process requires prolonged irradiation and can only generate milligram quantities of product due to a very low overall quantum yield. However, by performing this reaction in a flow photoreactor we were able to generate 1.4 g of **8** in a 7 h run.[5] Recently we reported[6] that a number of these photochemically-generated aziridines undergo a [1,5]-sigmatropic H-shift/ring-opening sequence, some at surprisingly low temperatures (<100 °C). Pleasingly heating **8** to just 100 °C in toluene gave the rearranged imine **12** in 86% yield. Importantly this rearrangement placed the alkene in the correct position for the key Heck cyclization of **7**. A reductive amination sequence of **12** with 6-iodopiperonal gave **7** in 64% yield. Although the yield may appear moderate, this sequence is somewhat impressive considering it involves an imine reduction followed by condensation of the resulting amine with the aldehyde and a conventional reductive amination sequence thereafter. Pd-catalyzed Heck cyclization of **7** proceeded cleanly using P(*o*-tol)$_3$ as ligand and DIPEA as base, giving the tetracycle **13** (R = $CO_2{}^tBu$) in excellent yield. No reaction occurred using other ligands (e.g. PPh_3 and $P(^tBu)_3$). Hydrogenation of the alkene over Pd/C gave **14** (R = $CO_2{}^tBu$) in 82% yield. In a highly efficient telescoped sequence the *tert*-butyl group in **14** was removed with TFA, the resulting crude acid decarboxylated by treatment with oxalyl chloride and finally the reactive iminium ion immediately reduced with $NaBH_4$ to give (±)-γ-lycorane **6** in 84% overall yield (380 mg). This represents an efficient and diastereoselective 6-step synthesis of **6**, which further highlights the synthetic utility of photochemically produced aziridines.

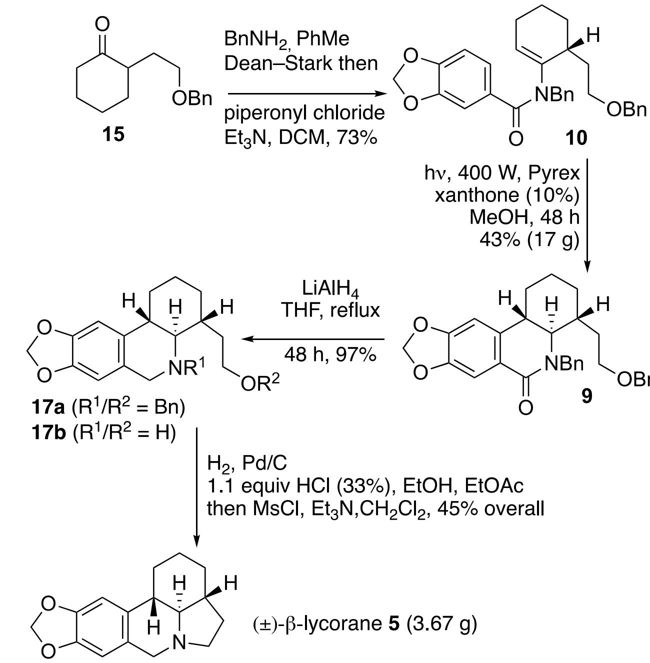
We were interested in exploiting the 6π-photoelectrocyclization[7] of enamides to isoquinolones to allow a similarly rapid synthesis of β-lycorane **5**. For example, irradiation of the enamide **10** (Scheme 1) should result in electrocyclization proceeding in a conrotatory manner which should furnish the isoquinolone derivative **9** with the requisite *trans*-fused stereochemistry at the two saturated six-membered rings in **5** (Scheme 1).

Scheme 2. Total synthesis of (±)-γ-lycorane 6.



Dean–Stark condensation of the ketone **15** with benzylamine followed by *in situ* reaction of the resulting imine with piperonyloyl chloride gave the enamine **10** in 73% yield. This reaction could be scaled up, yielding >50 g batches when required. The sensitized photocyclization of **10** was initially carried out on 100 mL scale using a Pyrex-filtered 125 W medium-pressure Hg lamp. Optimization of this reaction for maximum productivity initially proved challenging as the resulting product **9** was very sensitive to further oxidation to the corresponding dihydroisoquinoline **16**,[8] which itself underwent further degradation resulting in reactor fouling. By rigorous degassing before irradiation and continuous sparging with nitrogen throughout, the desired *trans*-isoquinolone **9** could be isolated in a combined 67% yield along with a diastereoisomer[8] and the aforementioned oxidized product in a 7:2:1 ratio respectively. Encouraged by this we scaled up the reaction to 1 L (41 g of **10**) and irradiated with a 400 W medium-pressure lamp, with rigorous oxygen exclusion, resulting in the isolation of 17 g of pure **9**.[9] Amide reduction with $LiAlH_4$ gave the amine **17a** (R_1/R_2=Bn) in 97% yield. Initially double debenzylation of **17a** (R_1/R_2=Bn) proved to be slow and incomplete. Repeating the hydrogenation with an equivalent of conc. HCl gave the desired product **17b** (R_1/R_2=H) in essentially quantitative yield (as the HCl salt) and with sufficient crude purity to telescope directly into the ring closure to afford **5**. Thus, 16 g of **17a** (R_1/R_2=Bn) was hydrogenated under acidic conditions and the crude amino-alcohol **17b** (R_1/R_2=H) cyclized with $MsCl/Et_3N$ to give 3.67 g of β-lycorane **5** in 45% overall yield from **17a** (R_1/R_2 = Bn).

Scheme 3. Total synthesis of (±)-β-lycorane 5.



In summary, the total synthesis of two members of the lycorine alkaloid family has been described. Although the two alkaloids differ only in the relative stereochemistry of one C–H bond, two completely different routes were conceived. These routes are short and scalable, and both involved photochemistry as a key step. The synthesis of (±)-γ-lycorane **6** was completed in six steps utilizing the high reactivity of the photochemically-produced aziridine **8** for the isomerization by a thermal [1,5]-sigmatropic H-shift. A highly efficient, telescoped final sequence yielded nearly 400 mg of the (±)-γ-lycorane from a simple pyrrole starting material. Using a 6π-photoelectrocyclization reaction of an enamide, the synthesis of (±)-β-lycorane **5** was completed in just four steps from the known ketone **15**. The brevity of this route enabled much larger quantities of product to be synthesized than is the norm for total synthesis; in this case 3.67 g of (±)-β-lycorane **5** was produced in a single synthetic run from **15**.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI:

Complete experimental procedures and compound characterization data (PDF)

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript. ‡These authors contributed equally: WLY synthesized (±)-γ-lycorane and TN synthesized (±)-β-lycorane.

ACKNOWLEDGMENT

We thank the EPSRC Bristol Chemical Synthesis Doctoral Training Centre (EP/G036764/1) and Lilly UK for PhD studentship funding.

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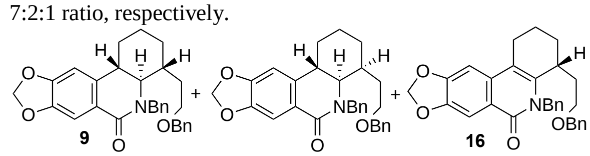
(8) The desired isoquinolone **9** was isolated as the major isomer along with its diastereomer and oxidized product **16** in a 7:2:1 ratio, respectively.



(9) A preliminary flow reaction required an almost static flow rate to get any conversion and therefore it proved less practi-

cal than batch. This is simply a very slow reaction that requires long exposure to UV.